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Forum

Retroactive Ethics in Rapidly Developing Scientific Fields

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Science often progresses faster than regulation, and retroactive ethically linked rules have been a persistent issue in stem cell research. Proposed NIH funding rules are retroactive. Legal history and ethical analysis show why there should be a strong presumption that such new rules should be only prospective, in any area of scientific research.

The National Institutes of Health (NIH) has just proposed draft embryonic stem cell (ESC) funding rules that, if adopted following an open comment period, few existing cell lines would meet. This constraint is due to new, specific mandates for informed consent. The proposed rules do not explicitly provide research funding for existing so-called Presidential ESC lines fundable under President George W. Bush, although some of these lines may yet be eligible under the current drafted regulations. Existing NIH grants are also not protected, raising the possibility that ongoing experiments must be interrupted, and new cell lines developed, for current research to continue. Nor do the proposed rules promise funding to the many ESC cell lines derived after 2001 according to ethical protocols approved by institutional review boards (IRBs), operating under federal regulations. Furthermore, funding for cell lines derived according to the so-called "NAS guidelines" (Committee on Guidelines for Embryonic Stem Cell Research, National Research Council, 2005) or the "ISSCR guidelines" (Human Embryonic Stem Cell Research Task Force, International Society for Stem Cell Research, 2006) will also be in jeopardy based on the proposed NIH requirements for consent documentation. The NAS and ISSCR guidelines were developed after extensive multidisciplinary deliberation, and public consultation over several years. The resulting guidelines are considered models of self-regulation, and they have been adopted widely across the global research community. Existing IRB reviews and the established guidelines ought, therefore, to be given significant weight when assessing the ethical provenance of an ESC line.

Prospectively applied, the proposed NIH rules as they stand would present a challenge to the field. But retroactively applied, the draft regulations would create a tectonic shift: previously, only certain *old* lines were fundable, and now—conceivably—only certain *new* lines will be, and there will continue to be no federal funding available for research using cells created ethically since 2001. Important research will need to be repeated, and assays and data rebuilt. As currently outlined, it's as if the last 8 years of cell line creation and ethical self-regulation have just vanished, to be replaced by a new funding structure that does not give weight to the existing science, ethics, self-regulation, donor intentions, or diverse cell lines. Resolving this situation is critically important for stem cell research. But the broader principle—should government guidance be retroactive?—is vital for all areas of scientific research.

Informed Consent under the Proposed Funding Rules

The proposed rules require nine consent elements to be documented in the written informed consent form for donors who release embryos for research purposes. Some requirements are traditional, and well-established in the research community, such as that consent was voluntary and the donor was aware of alternatives. Other requisites are newer, and while they may have merit, such as prohibiting directed donation and barring donors from receiving any financial gain from patents or products, these issues have yet to be publicly debated in depth. In addition, institutions must assure compliance in applications and progress reports and maintain the connection between noncompliance and potentially severe penalties (civil False Claims Act penalties and damages; criminal prosecution). Institutions will presumably be conservatively risk averse. Institutions must also assure that conditions in IVF clinics are documented, including at least two consents—at the time of seeking reproductive services and at the time of donation. While full consent at the time of donation is essential, neither the NAS nor the ISSCR guidelines require, in all cases, that there have been a previous consent form that avoids mention of hESC, as required by the proposed NIH rules. Consent must also have been revocable until the time embryos were "used in research," which, while reflective of some guidelines, can be problematic for deidentified donations, depending on how "use in research" is defined. Finally, clinics must have had policies in place to ensure that medical care was unaffected by the decision to donate, and uninfluenced by researchers or inducements. In this case, the key concern is not the avoidance of influence per se, which is important, but whether that practice must be reflected in a written policy, instead of, for example, corporate or departmental separation of researchers from the IVF clinicians.

Sugarman and Siegel (2008) and Lo et al. (2009) have persuasively argued that determining whether a given ESC line can be used ethically based solely on an informed consent form—the approach of the proposed NIH funding rules—is mistaken. Instead, contextual evidence of the consent process may be sufficient when an informed consent form does not itself document all elements that

modern guidelines require. The central inquiry is whether "investigators acted substantially in accord with underlying ethical principles (e.g., respect for autonomy)." Contextual evidence may include written policies, forms, and IRB minutes, but also expert opinion about consent standards of the time, investigator interviews, and knowledge of local review processes. For existing lines, the Sugarman/Siegel/Lo approach would reconcile the novelty of new ethical requirements with a realistic test about whether line provenance substantially meets ethical fundamentals. However, the authors' contextual approach is precluded by the present NIH proposal, which explicitly requires that specified elements be in the informed consent form itself, and that IVF practices and policy must be prospectively documented. Since the Sugarman/Siegel/Lo approach is thus unavailable to evaluate existing lines, we must confront the question of whether the blanket retroactivity of the proposed funding rules is justified.

Should the Proposed Ethical Rules Be Retroactive?

Retroactivity has been a persistent issue in stem cell research, and perhaps anywhere science progresses faster than regulation: when regulations catch up, there can be a disruptive effect on science that has been deemed fully ethical till that time. The NAS guidelines, for example, imposed new consent requirements for gamete donations and tissues for somatic cell nuclear transfer (SCNT) and did not "grandfather" existing well-characterized somatic cell lines that might have been suitable sources for disease-specific SCNT-created stem cell lines. Recently, Robert Streiffer accused the NIH of ignoring important consent fundamentals with respect to the Presidential lines; when the head of the NIH stem cell effort replied that Streiffer was imposing a retroactive standard, Streiffer responded that related standards had been discussed by various committees over time, and his arguments "derive[d] from" principles long recognized, even if in varying form (Baker, 2008). The result was uncomfortably inconclusive; review committees became divided about how to handle the criticized lines—whether to forbid them, permit them with special justification, or permit them completely as having met then-prevailing IVF standards. The field will face the same issues with iPSCs. Aalto-Setälä and colleagues have observed that new uses for iPSCs raise many consent issues, including chimeric uses, genetic modification, large-scale genome sequencing, transplantation, and reproductive research—uses not traditionally included in basic tissue consents except in research directed to such purposes (Aalto-Setälä et al., 2009). What iPSC uses will be permitted when consent documentation is absent, or incomplete, for the parental somatic cell lines? The scientific case for disease-specific studies may be compelling; should retroactive rules prevent such use?

Anglo-American law has debated retroactivity for centuries, and its insights are illuminating. U.S. law is historically hostile to retroactive enactments. A presumption of legal prospectivity has been a continuing feature, along with explicit constitutional constraints on retroactivity in certain areas. Common law opposed retroactivity because of absolutist monarchs, who occasionally attempted to punish treason, and take land and property, under new edicts applied retroactively. In the U.S., enlightenment commitments to personal liberty, individual property, and a just society fostered eloquently expressed protests against retroactivity, and not just for criminal laws. Retroactive laws were considered a form of "oppression," characteristic of "Roman princes," which the "fundamental laws of every free government" would condemn (*Dash v. Van Kleeck*, 1811; *Terrett v. Taylor*, 1815).

Neither *Terrett* nor *Dash*, nor the many other such cases of the time, was a funding case; widespread government funding is more recent. In varying contexts since then, retroactivity has had ups and downs. But underlying values continue: the presumption of prospectivity survives, except where courts must respect express or implied Congressional statements of retroactivity. Even then, retroactivity must pass constitutional muster.

Retroactive versus Prospective Laws

In a much-quoted definition among jurists, Justice Story of the U.S. Supreme Court, in the 1814 *Society for Propagating the Gospel* decision, defined a retroactive law as one that "takes away or impairs vested rights acquired under existing law, or creates a new obligation, imposes a new duty, or attaches a new disability in respect to transactions or considerations already past" (*Society for Propagating the Gospel v. Wheeler*, 1814).

Later cases clarified that laws can be retroactive in two ways. First, they can explicitly affect past conduct, such as by making a past act criminal, or through a retroactive effective date. Second, they can be retroactive by changing the future consequences of past actions. Thus, one way the current proposed NIH rules are retroactive is that grants previously awarded to use certain Presidential lines are apparently no longer eligible for funding, despite the previous grant agreement and expectations of scientists.

There are also two ways in which a law may be purely prospective. First, it may apply explicitly only to future transactions. A second kind of prospectivity is "grandfathering," i.e., an explicit recognition that new rules should not disadvantage existing categories. Grandfathering can be conditional or unconditional, and either unlimited or limited in time or scope. Waiving new consent rules for all existing stem cell lines derived from surplus IVF embryos, provided they met ethical standards of the time, would be one form of grandfathering. Alternatively, grandfathering might be conditioned on IRB or ESCRO approval, or it might limit grandfathering for a time, say 3 years, so that a suitable number and diversity of new lines could be developed using new consent standards.

What's Wrong with Making the Proposed NIH Rules Retroactive?

Why would retroactive application of the proposed consent rules be problematic? First of all, not everyone may agree with the rules, as currently drafted, and so making them retroactive worsens the situation. Scientists might believe that the NIH is misbalancing competing interests between scientific benefit and consent standards, or some ethicists may think the consent standards are wrong in other ways. But I will leave those issues for others to discuss, as there are special problems with retroactivity itself to consider at present.

First, affected parties are deprived of any notice that would allow them to conform their conduct to new requirements. For example, it is too late for IVF clinics to incorporate new consent terms

in old informed consent documents, particularly if deidentifying to protect privacy prevents donor recontact and reconsent. It is too late for scientists to rewrite protocols and turn back the clock on derivation research. What might have been possible, if known in advance, is now impossible.

Second, as reflected in Justice Story's comment, retroactive rules violate the sense that certain rights are "vested"; vested means that the rights deserve special respect because of their duration, compliance with rules and expectations of the time, or government's or others' conduct in confirming them. Affected parties acquire a certain "right," such as to conduct funded research with a given cell line, if government, society, or ethical culture confirmed at the time that their behavior was ethically adequate. We'll see how this applies below.

Third, retroactive provisions undercut reliability, not just as to their particular subject matter, but as to the whole system of regulation: if retroactive provisions are permitted, then even the new retroactive rules, and in fact any rule, is subject to being overturned through yet one more, later, retroactive rule. Will the new NIH rules, in whatever form they are finalized, be rewritten retroactively with every new administration, or scientific advance?

Fourth, retroactive rules, even stated neutrally, are easily targeted to disproportionally disadvantage known populations. "Neutral" rules that shift funding from one politically favored group to another are easier given retrospective data. I do not think that is a tenable claim about the current NIH proposal—to the contrary. But we have just emerged from an era of politics directed at control of science. So this is important: are retroactive rules a wise course for government regulation of science under diverse political leadership?

Finally, recall how Common Law saw retroactive laws as potentially inconsistent with free societies. In this regard, jurist Lon Fuller observed that absent special circumstances, such as fixing legal mistakes, a retroactively applicable rule is "a monstrosity," a deviation from law's fundamental morality of prospective enforcement, so that even enactment by proper organs of government could not truly make it a "law" (Fuller, 1969). We'll return to this also.

It is useful to translate these points into familiar ethical terms. There are autonomy interests of donors. But this consideration is ambiguous: even if the proposed consent requirements protected donors better, some existing cell lines would be made useless, even if donors would have wished them used. There are important interests in maximizing stem cell resources for social benefit. Defining this interest is also ambiguous if, giving the proposed rules the benefit of any doubt, there is a trumping social benefit from using only stem cell lines that pass new ethical muster. However, it is difficult to see what ethical superiority lies in the documentary requirement that provisions be restricted to information on the informed consent form, if equivalent provisions and participant acceptance are as well documented via contextual evidence.

There is a justice interest in treating like cases alike going forward, so that all funding decisions (and grantees) are subject to the same rules. But not all cell lines *are* alike: those ESC lines created in accord with rigorous ethical rules of the time deserve to be treated differently from lines (like the Hwang lines of several years ago) created with less attention to ethical fundamentals or prevailing standards.

There is also a justice interest in keeping commitments to scientists who received grant awards. In addition, it is unjust to create new IVF consent rules to which, being retroactive, one has no opportunity to conform. Moreover, while scientists could not reasonably claim a "vested right" to funding (except under existing grants), it is not an overstatement that scientists and donors could reasonably rely, for an ethical stamp of approval, on (1) government designation of Presidential lines (recently reapproved by government); (2) federally regulated IRB review; and (3) review under NAS and ISSCR standards, standards to which the NIH has not objected and, I must believe, the NIH would not now condemn. So why can't scientists rely on lines that fall into these categories?

Finally, there is an issue of global justice. The new rules apply, as drafted, to ESC lines created anywhere in the world. Lo et al. (2009) have suggested a method for evaluating cell lines that would not meet local (evolving) standards, through reference to core principles, but the present NIH proposal would preclude that approach. Unless new U.S. IVF consent procedures are implemented internationally, the U.S. will make no funded contribution to the use, characterization, and development of ESC lines from abroad. Given the geographic differences in prevalence of genetic diseases, any preclusion of international cell lines is perhaps a tragic message for U.S. investment in nondomestic health.

Ethics scholars have added "community" as a fourth ethical factor, where one must consider the implications of a proposal on the wishes, risks, and benefits for specific communities (Emanuel and Weijer, 2005). Here, "community" relates to the historic view that retroactivity violates fundamental interests of free societies, which are broader than individual autonomy interests or social goals of stem cell funding itself. While it has been a long road, the ethics and scientific communities have converged around a set of ethical standards and review procedures, as evidenced by the broad adoption of both NAS and ISSCR guidelines, among others. The proposed NIH rules discount the national and international community investment and interest in those standards, as well as the community processes that led to them.

There is another way of looking at the community question: At what point do ethics statements represent a sufficient social consensus that it becomes fair for a community or government to charge individuals with retroactive obedience through regulations? Is it when some ethicists (or lawyers, like me) have written some papers, in an ethically contested landscape? Is it even when ethicists agree among themselves, whether or not engagement with the scientific community or robust and inclusive public engagement has occurred? The key purpose of democratic institutions and procedures is to guarantee public engagement in lawmaking; one should therefore question whether ethics, without engagement, should have the force of law without having undergone its democratic rigors (Taylor, 2007). Justice Story would have complained in stronger terms and held that retrospective ethics, even if delivered by government, are an oppression that Magna Carta and the schisms of the Reformation and Restoration had taught

us to avoid. One need not go to that extreme, however. When Lo et al. (2004) and others wrote seminal papers elevating our conception of required consent, they were saying new and important things, not just describing an existing consensus. It took time for bodies like the NAS and ISSCR to discuss and develop consent guidelines, while IRBs were meanwhile acting to protect donors by adapting and applying federally promulgated regulations long in the making. Thirty days notice and comment *after* rule development is not the same as years of deliberation and engagement *before* rule development. The NIH proposal, while partly foreshadowed in the Clinton era, is only weeks old, and the Clinton-era proposal was one version among others contending for approval. I think, therefore, that the novel terms contained within the proposed rules are neither sufficiently established nor created through sufficient past engagement to warrant retroactive application.

Conclusion

The proposed rules should be modified. They should not be retroactive. Grants awarded previously should be continued, and Presidential lines ought to be eligible for funding. Funding should be permitted for ESC lines created previously if approved by IRBs or ESCROs under the standards then applicable, and for new cell lines derived from embryos donated ethically under IRB-approved protocols and then-existing standards, including the NAS and ISSCR guidelines. The rules ought to allow the Sugarman/Siegel/Lo framework to operate: the NIH should permit contextual evidence of adherence to ethically core principles, including for research using lines that originate outside the U.S.

Rules and guidelines will often trail rapidly developing science (Rugg-Gunn et al., 2009; Marchant and Pope, 2009). To justify the retroactive application of new rules to scientists, institutions, and donors, proposed changes should be held to an ethical consensus that is sufficiently established, inclusive, and attentive to democratic protections, and that meets squarely each of the concerns outlined above. Those concerns should create a presumption against retroactivity *especially* in rapidly developing and ethically contested fields of science, for it is precisely in that arena that debate must be encouraged, but without fear of unfair retroactivity. All rules should be subject to exceptions—atrocities should always prompt swift action—but precisely because of the clear moral footing of the objection. The varying, good-faith versions of existing, and proposed, appropriate stem cell consent do not fall into the category of morally objectionable.

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